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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,518	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/05; 3/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3 are canceled.

2. Claims 4-17 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections Withdrawn

4. The objection to the title as not being descriptive of the claimed invention is withdrawn in view of the newly submitted title filed 3/6/06.

Response to Arguments

5. The rejection of claims 4-17 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained.

Applicant again summarizes the examiners potion, the disputed issues, cites case law and MPEP. Applicant also reviews the legal standard for utility, with which the Examiner again takes no issue. Applicant maintain that the asserted patentable utility of the PRO1864 polypeptide is based on the disclosure in Example 18 of the instant application that the mRNA encoding the PRO1864 polypeptide is "more highly expressed" melanoma tumor compared to normal skin.

Beginning at page 10 of the response, Applicant argues the differential expression of PRO1864 mRNA was detected using the technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissues samples. Applicant argues that identification of the differential expression of the PRO1864 polypeptide-encoding gene in tumor tissues as compared to the corresponding normal tissue "renders the molecule useful diagnostic tool for the determination of the presence or absence of tumor." (pg 10). It is further asserted that because it is well established that changes in mRNA levels lead to changes in the level of the encoded protein, one would expect the PRO1864 protein to be differentially expressed in melanoma tumor compared to normal skin. Applicant argues that anti-PRO1864 antibodies may be used in diagnostic assays for PRO1864 (polypeptide), e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues or serum.

Applicant's arguments have been fully considered but are not found persuasive for the following reasons. An assay using PCR amplification as described in Example 18, the Appellants merely measure the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO:14. There is no evidence regarding whether the level of PRO1864 polypeptide of SEQ ID NO:14 is more highly expressed in melanoma compared to normal skin. The specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed PRO1864 polypeptide of SEQ ID NO:14, nor does it establish that the expression of PRO1864 is melanoma specific. Thus, there is insufficient information or experimental

data presented on whether the polypeptide or the antibodies binding such (SEQ ID NO:14) of the present invention can serve as a reliable diagnostic marker for melanoma tumor. Moreover, the assay does not establish a causative link between the polypeptide (or antibodies) of the present invention and melanoma tumor. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of melanoma tumor without further experimentation. The information disclosed in the instant specification is preliminary at best as there is no evidence or data that a change in PRO1864 mRNA or polypeptide expression is tumor-dependent, consistent and measurable. Finally, the art indicates that the changes in mRNA expression do not correlate with polypeptide levels (e.g., Haynes et al, Gygi et al and Gokman-Polar et al, Greenbaum et al, Lian et al, Fessler et al, Hanash [a] and Hanash [b], evidence of record). Clearly further research would be required to reasonably confirm the real world context of the asserted utility, i.e., whether the PRO1864 polypeptide or antibodies binding the polypeptide can serve as a reliable diagnostic marker for melanoma tumors or as a therapeutic target for treatment of melanoma tumors. Accordingly, the claimed utility is not substantial.

From pp. 10-15 of the response, Applicant refers to the declaration of Mr. Grimaldi filed under 37 CFR 1.132 (Exhibit 1, filed 4/29/05) and argue against the Hu et al and LaBaer references and cites the art of Kuo et al. Further it is asserted by Mr. Grimaldi that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates

that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, i.e., to screen samples to differentiate between normal and tumor". It is further asserted that the PTO's assertions are contradicted by Mr. Grimaldi's statement, "the precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." Applicants' assert that this declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression is in normal tissue is irrelevant. Further, applicants' argue that Mr. Grimaldi states that if a difference is detected using these techniques, "this indicates that gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes." (pg. 11). Thus, applicants' contend that it is the uncontested opinion of an expert in the field that the results are reliable enough to indicate that the claimed antibodies are useful as diagnostic tools. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a approximately 2-fold amplification of the

message amplification (mRNA) (as suggested by the declaration) encoding PRO1864 is significant. However the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. It remains on this record that Hu et al analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The specification fails to disclose any specific "fold amplification" that is required between normal and cancerous tissue for a diagnostic determination. Is a 1-fold, a 5-fold, a 10-fold, or a 100-fold difference required? If the "fold amplification" were disclosed in the specification to be 100-fold, for example, then the cDNA that encodes the PRO1864 polypeptide would likely have a specific and substantial utility as a diagnostic marker for melanoma tumors. However, such is not the case here. Most importantly, an assay using cDNA analysis as described in Example 18 merely measures the mRNA level; the chemical intermediate involved in translating DNA into protein and tracking this middle step reveals nothing about protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of diseases. Importantly, Example 18 does not measure the over-expression of the PRO1864

polypeptide of SEQ ID NO:14 or antibodies that bind to the polypeptide of SEQ ID NO:14. Regarding the interest of the expert in the outcome of the case, it is also noted that the expert has interest in the outcome of the case, since Mr. Grimaldi is listed as an inventor and is employed by the assignee.

Applicant again criticizes the publication of Hu et al and claims that the observations of Hu et al are due to the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors, citing a statement from the article (3rd paragraph of left column of page 412) as evidence. Thus, it is the contention of the Appellants that because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially expressed gene exists. Further, Applicants' argue that Hu et al do not say that a correlation in their study means that genes with less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer. Applicants' arguments have been fully considered but are not found persuasive for the following reasons.

Hu et al teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold change or more are likely to be related to breast cancer and warrant attention (2nd

paragraph of left column of page 412). Hu et al teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). Hu et al states clearly: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405). Further, it is reiterated that LaBaer teaches that reports of mRNA or protein changes of as little as two-fold are not uncommon and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between samples. In view of the limited disclosure in the instant case, lack of disclosure of the "fold amplification" that was used to determine whether a higher expression, i.e., "more highly expressed" was significant, lack of the statistical analysis, and lack of establishment of a correlative link between gene expression and protein level or a causal link between mRNA expression and melanoma tumour, the teachings of Hu et al and LaBaer support the examiners position that further research is needed to reasonably identify or confirm a substantial utility for the instantly claimed polypeptide of SEQ ID NO:14 (PRO1864) and the antibodies binding the polypeptide. Further, it is curious that the Grimaldi declaration (discussed above) is relevant to the utility of the claimed invention, yet the cited art of

Hu and LaBaer are irrelevant according to applicant. The Grimaldi declaration and the art of Hu and LaBaer are limited to gene expression and not polypeptide levels.

In response to the Examiner's argument in the previous office action, Applicants summarize the second portion of their argument as such: "it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1864 polypeptide in melanoma, it is more likely than not that the PRO1864 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic and therapeutic tools" (pg. 16; emphasis by Applicants). Applicants argue that the references cited in the rejection are either irrelevant, not contrary to Applicants' arguments or actually offer support for Applicants' position. These references include Haynes (1998); Gygi (1999); Alberts [a] (2002); Alberts [b] (1994); Lewin (1997); and Zhigang (2004). In support of their argument, Applicants further turn to support from previously submitted declarations and references and from newly submitted references (pg 30-36).

Applicants' arguments have been fully considered but are not found to be persuasive. The previously and newly cited references submitted by Applicants in support of their argument have been fully considered. It is clear that the correlation between protein and mRNA levels is an active area of investigation and different studies have reported conflicting results. However, given full consideration of the previously submitted references, newly submitted references, and the relevant art, the Examiner

does not find Applicants' arguments to be persuasive. Each argument will be addressed in turn.

With regard to the references of Haynes and Gygi, Applicants argue that these studies only provide teachings regarding the predictability of the correspondence of steady-state mRNA and protein levels, and do not speak to whether or not a detectable change in mRNA level will lead to a detectable change in protein level, and therefore are not relevant to Applicants' argument. The Examiner finds these arguments persuasive. The Examiner agrees with Applicant that these references do not provide teaching as to whether changes in mRNA expression are generally reflected as changes in protein expression. Applicants' arguments appear to distinguish the instant case from the data provided in Haynes and Gygi in that Haynes and Gygi disclose that similar mRNA levels for different genes did not universally result in equivalent protein levels for the different gene products, and similar protein levels for different gene products did not universally result from equivalent mRNA levels for the different genes. Applicant notes that these results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Thus, applicant acknowledges that there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein, yet applicant presumes that an increase in PRO1864 mRNA levels would lead to a corresponding increase in PRO1864 protein levels. However, applicant has not characterized PRO1864 to an extent to reasonably conclude that PRO1864 is precluded from the many factors that determine translation efficiency for a given

transcript, or the half-life of the encoded protein. Further, while applicant is critical of Haynes and Gygi for not studying the issue that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein, it is applicant that has not provided data that increased PRO1864 mRNA leads to a corresponding increase in PRO1864 protein levels. Further, applicants' argue that Greenbaum state that there is a high degree of correlation between mRNA and protein levels for ORFs that show a large degree of variation in their expression (see Greenbaum at top of pg. 117.5) and applicant reiterates that while transcriptional regulation is not the only mechanism for controlling protein levels, transcriptional regulation is the predominant mechanism for regulating protein levels. This has been fully considered but is not found persuasive. While Greenbaum acknowledges a correlation between mRNA and protein levels for those ORFs that show a large degree of variation in their expression, it is not known whether PRO1864 shows a large degree of variation in expression. Further, continuing on pp. 117.5-117.6, Greenbaum teach that protein turnover can vary significantly depending on a number of conditions; the cell can control the rates of degradation or synthesis for a given protein, and there is significant heterogeneity even within proteins that have similar functions.

Applicants also contend that the relevant art does teach a correlation between mRNA and encoded protein levels; in support of this argument Applicants submit Exhibits 14-21, containing a total of 33 references (pp. 34-35).

Applicants' arguments have been fully considered but are not found persuasive. With the exception of Exhibit 13 (Futcher), Exhibits 13-20 are all directed to analysis of

single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. A more comprehensive analysis like Haynes (80 proteins examined), Gygi (150 proteins examined), Chen et al (Molecular and Cellular Proteomics 1(4):304-313, 2002, Ids reference 7, filed 9/30/05) (164 proteins examined) or Futcher (148 identified proteins) more accurately describes general trends. The Examiner agrees with Applicants that Futcher is a study similar to Gygi but reaches different conclusions that Gygi. However, Futcher also teaches, "the correlation is far from perfect, there is at least a 10-fold range of protein abundance" (pg 7360) and "Despite generating broadly similar data, Gygi et al reached markedly different conclusions... Gygi et al feel that mRNA abundance is a poor predictor of protein abundance... These different conclusions are partly a matter of viewpoint. Gygi focuses on the fact that the correlations of mRNA and codon bias with protein abundance are far from perfect, while we focus on the fact that, considering the wide range of mRNA and protein abundance and the undoubted presence of other mechanisms affecting protein abundance, the correlations are good" (pg 7367 of Futcher, 1999. Molecular and Cellular Biology. 19(11): 7357-7368; Applicants only submitted the abstract of Futcher; the Examiner has placed the entire Futcher reference on the PTO-892 attached to this Office Action). For these reasons, the Examiner maintains that these references demonstrate the mRNA levels do not necessarily correspond to protein levels, although as noted above the Examiner acknowledges that these references do not address whether observable changes in mRNA levels will be reflected as observable changes in protein levels.

With regard to the Lian and Fessler references, Applicants argue that although the authors characterize the mRNA and protein levels as showing a poor correlation, this does not reflect a lack of correlation between a change in mRNA level and a corresponding change in protein level. Applicants argue (pg 26) that of the 28 differentially expressed proteins identified by Lian, only one that is differentially expressed at the mRNA shows a corresponding change in protein level. Applicants further argue (pg 28-29) that Fessler identifies 6 differentially regulated proteins that also show a change in mRNA expression, of which 5 show a similar change, and that this actually supports Applicants' argument.

These arguments have been fully considered but are not found persuasive. In contrast to Applicants' arguments, the Examiner considers the results in Lian and Fessler to support the position that changes in mRNA do not necessarily reflect changes in protein level. Applicants' arguments focus on the proteins that were noted to have a change in protein expression. However, in both studies, the researchers found a large number of transcripts that were differentially expressed than proteins that were differentially expressed. Lian characterized 837 transcripts that changed substantially during MPRO (promyelocytic cell) differentiation (pg 515). In view of the 837 transcripts that were differentially expressed, it is significant that only one of 28 identified proteins (out of 50 that were noted to be differentially expressed) showed a corresponding change in mRNA. If, as Applicants argue, that changes in mRNA generally lead to changes in protein level, one would expect many more of the 837 differentially expressed transcripts to be identified as a differentially expressed protein. Similarly,

Fessler identified 100 genes that were upregulated in human neutrophils exposed to bacterial lipopolysaccharide (LPS) (pg 31293 and Table I), but only identified 8 proteins that were upregulated to a statistically significant degree (pg 31393 and Table III).

Applicants refer to previously submitted declarations and references in support of their arguments that changes in the level of mRNA correspond to changes in the level of the encoded protein (pg 19-22). The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of Alberts [a], Alberts [b], Lewin, Zhigang and Meric support the statements of Grimaldi and Polakis.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts [a], [b] and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts [a], [b] and Lewin also teach that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms. Furthermore, while Zhigang provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen,

more comprehensive studies (Lian and Fessler, discussed above; Nagaraja (2006), Waghray (2001), and Sagynaliev (2005), cited below) show a different general trend. Applicants also have submitted Meric et al., 2002, which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

Meric et al also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974).

In addition to the previously submitted references, Applicants submit 81 new references (Exhibits 2-12) in support of their argument (pg 30-34). These references have been fully considered by the Examiner but are not found to be persuasive. First, except for the Orntoft reference (cited at pg 30), each of the references submitted by Applicants is directed to a single gene, or a small number of genes. These references are consistent with Gokman-Polar et al who found some proteins do show correlation between mRNA and protein. However, these studies examining the expression of small numbers of genes are not found persuasive in view of comprehensive studies where

significantly larger numbers of transcripts and proteins were examined, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2006) which are described below.

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one.

Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft compared the mRNA and proteins levels of about 40 well-resolved and focused abundant proteins with known chromosomal locations (see pg 42). The instant specification does not teach whether or not PRO1864 is a "well focused abundant" protein with a known chromosomal location as characterized by Orntoft. Furthermore, other relevant publications (Nagaraja (2006), Waghray (2001), and Sagynaliev (2005)) report that increases in mRNA and protein samples are not correlated (see below).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies comparing changes in expression of the transcriptome and proteome support this argument. Nagaraja (2006) teaches, "We have characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231)...the proteomic profiles indicated altered abundance of few proteins as compared to transcript profiles" (See abstract of Nagaraja, 2006, Oncogene. 25: 2328-

2338). Nagaraja further teaches, "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (pg 2329) and "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (pg 2335). Similarly, Waghray (2001) teaches, "we have analyzed gene expression changes induced by dihydrotestosterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels" (see Abstract of Waghray, 2001. Proteomics. 1: 1327-1338). Waghray identified transcripts from 16570 genes and found "351 genes were significantly altered by DHT treatment at the RNA level." Waghray identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Twenty-nine of these proteins were identified and "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (Table 4)". If changes in protein generally reflected mRNA changes, based on the fact that 2% of the genes analyzed had a change in transcript levels (351 out of 16570 genes), one would expect at least 2% of protein levels to change, or 22 out of 1031 protein spots. Therefore, it is significant that while Waghray found 44 proteins that did change, very few of the identified ones had a similar change in mRNA expression.

In a review of gene expression in colorectal cancer (CRC), Sagynaliev (2006) teaches, "One thousand two-hundred and forty genes have been reported to be dysregulated (up- and/or down-regulated) in human CRC, representing about 5% of the 20000-25000 human genes" (pg 3067). Sagynaliev also teaches, "a total of 408

proteins were found to be differentially expressed in human CRC in at least one study" and importantly, "It is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support that changes in mRNA expression frequently do not result in changes in protein expression. Therefore, the Examiner maintains that Applicants' measurement of an increase of PRO1864 mRNA does not provide a substantial utility for the encoded protein, or an antibody to the protein.

Further, in response to the cited art of Hanash [a] and Hanash et al [b], applicant acknowledges that gene expression is regulated at numerous levels, however, applciant states that the declarations and supporting references supplied make it clear that regulation of mRNA levels is the predominant mechanism of control for the majority of genes. This has been fully considered but is not found persuasive. Again, Hanash [a] indicates that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Additionally, Hanash et al [b] states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). Thus, while the art, applicant and the examiner agree

that initiation of transcription is the most common point for a cell to regulate the gene expression (see Alberts [a], [b] and Lewin above), the art clearly recognizes that gene expression is also regulated post-transcriptionally. In view of the totality of the evidence the skilled artisan would not reasonably presume that the PRO1864 polypeptide is "more highly expressed" in melanoma tumor compared to normal skin based on the disclosure regarding PRO1864 mRNA expression without actually testing for PRO1864 polypeptide expression. Further experimentation would be required to determine whether a change in PRO1864 mRNA or polypeptide expression is tumor-dependent, consistent and measurable The requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form. One skilled in the art would do further research to determine whether or not the PRO1864 protein was overexpressed in melanomas compared to normal skin tissue. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. M.P.E.P 2107 I states:

> A '"substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In view of the totality of the evidence, the rejection for lack of utility is proper and is maintained.

6. The rejection of claims 4-17 under 35 U.S.C. 112, first paragraph, is maintained. As discussed above, since the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

7. The rejection of claims 4-5, 12-17 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is maintained.

The response filed 3/6/2006 has been carefully considered, but is deemed not to be persuasive. Applicant again reviews the evidentiary standard regarding the legal presumption of written description. The examiner again takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of written description. As argued previously the present response reiterates that the claims have been amended to recite that the claimed polypeptides have at least 95% amino acid sequence identity to several polypeptides related to SEQ ID NO:14 and in view of this high homology, the disclosure of SEQ ID NO:14 is sufficient to describe the claimed polypeptides. Applicant also argues that the specification discloses how to make the claimed polypeptides and methods of making variant polypeptides are well known in the art. This has been fully considered but is not found persuasive. Applicant is reminded that *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed.

Cir. 1991) makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). See MPEP 2161. Thus, applicant's arguments on how to make and use the polypeptide variants go more towards enablement and not the disputed issue of lack of adequate written description. Further, applicant's arguments that the instant case is similar to Example 14 of the written description guidelines and that there is not substantial variation within the claimed species of polypeptides have been fully considered but are not found persuasive. With respect to example 14 of the written description guidelines, the instantly claimed polypeptide of SEQ ID NO:14 is disclosed as being encoded by a nucleic acid more highly expressed in melanoma compared to normal skin, however, SEQ ID NO:14 has not been identified as having any particular biological function or activity that could distinguish members of the genus from those excluded. This is not similar to example 14 of the guidelines, which requires a protein (i.e., SEQ ID NO:3) and a particular biological activity. Further, the instant claims are drawn to polypeptides having 95% identity to the recited portions of SEQ ID NO:14. Applicant is invited to point out in example 14 of the guidelines where it is disclosed that polypeptides having 95% identity to portions of SEQ ID NO:3 are said to have adequate written description. Again, applicant is relying on the disclosure of a nucleic acid (mRNA) encoding the polypeptide of SEQ ID NO:14 that is more highly expressed in melanoma compared to normal skin, to support a genus of polypeptides related to SEQ ID NO:14 and portions and fusions of SEQ ID NO:14, which are not disclosed as having any particular biological function or activity. Additionally, it is reiterated that the specification does not

disclose any polypeptide that is 95% or 99% identical to SEQ ID NO:14 or portions thereof that are more highly expressed in melaonoma compared to normal skin tissue. Conception does not occur unless one has a mental picture of the structure of the molecule, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

The response argues with the case law of *In re Wallach* stating that the facts are similar to the instant case. This has been fully considered but is not found persuasive. The facts in *In re Wallach* indicate that possession of a complete amino acid sequence of a particular protein may put the inventor in possession of a genus of DNA sequences encoding it. The instant case differs in that the present claims are drawn to a genus of polypeptides and not a genus of DNA sequences encoding a particular protein sequence and the rejection does not challenge whether applicant has adequate written description of the genus of DNA sequences that encode SEQ ID NO:14. Thus, it remains on this record that there is insufficient written description for the claimed genus of polypeptides whose structures and functions may differ greatly from that of SEQ ID NO:14.

8. The rejection of claims 4-17 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 3/6/2006 has been carefully considered, but is deemed not to be persuasive. With respect to the polypeptide variants encompassed by the claims, applicant argues that one does not need to know what the consequence of the differential expression is in order to exploit this differential expression to distinguish tumor from normal tissue or to utilize antibodies against the claimed polypeptides to treat cancer. Applicant also reiterates that there is not substantial variation within the sequences of the claimed polypeptides and even if a particular mutation impacts a polypeptide's biological activity, one or more antigenic epitopes would be preserved such that antibodies raised against the variant polypeptide would recognize the polypeptide of SEQ ID NO:14 and could be used as diagnostic tools for melanoma. This has been fully considered but is not found persuasive. The examiner maintains in view of the evidence of record (Burgess et al, Lazar et al, Schwartz et al, Lin et al and Li et al) that while it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites.

For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980, of record)) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Applicant has not provided any guidance to assist the skilled artisan in making and using the claimed polypeptide variants that are 95% or 99% identical to SEQ ID NO:14 much less variants that are 95% or 99% identical to amino acids 21-53, 119-129 or 167-234 of SEQ ID NO:14 or fusion of said portions of SEQ ID NO:14 to the signal peptide of SEQ ID NO:14 (i.e., amino acids 1-20 of SEQ ID NO:14) in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments. Thus, given the substantial variability of the claimed polypeptides relative to the polypeptide of SEQ ID NO:14 and in view of the teachings of Lederman et al and Li et al (as well as Burgess et al, Lazar et al, Schwartz et al and Lin et al), it is unpredictable in the art which regions of the polypeptide of SEQ ID NO: 14 are tolerant to change and which regions are relatively intolerant to change. Further, complicating the issue is that the polypeptide of SEQ ID NO:14 has not been demonstrated to be more highly expressed in melanomas compared to normal skin. The teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention; they do not provide sufficient guidance or specificity as to how to execute that plan. At most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention.

Due to the large quantity of experimentation necessary to generate the polypeptide variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art (Burgess et al, Lazar et al, Schwartz et al, Lin et al and Li et al, previously cited in the Office Action mailed 1/31/2005 and Lederman et al), which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

9. The rejection of claims 4-6, 10 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as introducing new matter into the claims is maintained.

The response filed 3/6/2006 does not address this rejection and as such is maintained for reasons of record.

Conclusions

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER